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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,008	05/06/2002	Steven K Libutti	14014.0322U2	3848

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
11/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,008	LIBUTTI ET AL.	
	Examiner	Art Unit	
	Michael Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-19,22-37,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *3,5-15,17,19 and 23-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4, 16, 18, 22 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/22/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment dated 8/7/2008 is acknowledged. After entry of the amendment, claims 2-19,22-37,39 and 40 are pending, claims 3,5-15,17,19 and 23-37 remain withdrawn, and claims 2, 4, 16, 18, 22 and 40 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 103

Claims 2, 4, 16, 18, 22 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (U.S. patent 6,638,502, of record) in view of Restifo et al (U.S. patent 5,733,548, of record). **This rejection is maintained for reasons made of record in the Office Actions dated 2/22/2006, 11/9/2006, 6/13/2007, 2/8/2008, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 8/7/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Restifo et al only use the E19 ss to express short peptides; 2) there is no evidence that the E19 ss can direct secretion of any heterologous protein; 3) Martoglio et al (cited by the Examiner) points out that signal sequences can vary in their efficiency, and that it is not clear signal sequences work by the same mechanisms; 4) there are numerous instances where substitution of signal sequences results in reduced secretion; 5) the teachings of Li et al are limited to local delivery, and Restifo et al do not teach antiangiogenic proteins; 6) there is no expectation of success in using a viral vector to deliver endostatin linked to the E19 ss; 7) nothing in the prior art suggest arriving at a composition that reduces tumor

growth when administered systemically; 8) Griscelli et al does make up for the deficiencies of Restifo and Li et al.

Regarding 1) and 2), Restifo et al indicate the signal sequence may precede another peptide from 5 to 1000 amino acid resides (column 4, lines 32-40). Prior art is presumed to be enabling, absent evidence to the contrary, see MPEP 2121. Applicants present no reasoning or evidence as to why expression of a heterologous polypeptide using the E19 signal sequence as taught by Restifo et al would be unexpected. Indeed, the signal sequence naturally directs the expression of a 19 kD protein, (hence the name E19). The adenovirus from which the E19 ss of Restifo et al is derived is a human adenovirus and has thus evolved to replicate in human cells. Again, absent evidence to the contrary, the E19 ss is thus functional in human cells (the primary purpose of the instant specification is human therapy), at the very least. Thus, it is no great leap in science, or logic, in light of the prior art of record, that the E19 ss should be functional to direct secretion of a heterologous protein in human cells, at the very least. What would be surprising is if it did not direct secretion.

Regarding 3), it is not clear, and applicants do not explain, why the discussion signal sequences and their efficiency mitigates against the instant rejection, which involves an adenoviral ss which has evolved to be functional in human cells, and is evidenced by the art of record to secrete heterologous proteins. Furthermore, there is no discussion about the relevance of the signal sequence mechanism to the instant rejection. Why does this mitigate against the prior art when the prior art is clearly functional? Why does the skilled artisan need to know the exact molecular details when the relevant E19 ss is clearly a functional ss in human cells?

Regarding 4), conclusory statements are not convincing in light of the facts and evidence provided by the prior art of record. The art which applicant relies upon (e.g. Rowland et al) has not been made of record and thus any teachings within not considered. Furthermore, it is not explained why bacterial signal sequences are relevant to the instant rejection, which concerns a mammalian signal sequence. None of the references cited by applicants purport to use the E19 ss of the claims, nor do they directly refute the teachings of Martoglio et al.

Regarding 5) and 6), the prior art clearly indicates that the E19 ss is functional to direct the secretion of heterologous proteins/peptides. Thus given the teachings of the prior art, one of skill in the art could predictably use this signal sequence to direct secretion of antiangiogenic proteins from an adenoviral vector in a eukaryotic cell. Furthermore, the totality of the prior art teaches that antiangiogenic proteins can be expressed using signal sequences other than those "naturally" associated with the antiangiogenic protein. There does not appear to be any concrete obstacle to the use of the E19 ss to direct secretion of, for example, endostatin. Applicants rely upon unsupported and imagined problems, and continuously fail to present any reasoning or evidence, other than that the E19 ss was used by Restifo et al to express only small peptides, as to why expression of a heterologous polypeptide using the E19 ss would be unexpected. The same is true for the conclusory statement that there is no expectation of success when using the E19 ss to express endostatin in the context of an adenoviral vector in order to achieve the intended use recited in claim 40. All of the evidence provided by the Examiner points in the opposite direction, i.e. that there are no barriers to the predictable combination of Restifo and Li et al to arrive at the claimed invention.

Regarding 7), again, this is an intended use limitation and has been addressed previously. The composition taught by the prior art meets all the structural limitations of the claims, and thus meets the intended use limitation. Furthermore, absent evidence to the contrary, the use of the adenoviral E19 ss sequence to express an antiangiogenic protein in the context of an adenoviral vector would result in increased levels of circulating antiangiogenic protein relative to organisms/animals that did not receive the adenoviral vector, or received a control vector not expressing the antiangiogenic protein. The results of Griscelli et al, and applicants Exhibit C (submitted with the Pasqualini declaration, 12/14/2007), page 1018, third column, first full ¶, teach the general reduction in tumor size upon administration of viral vectors expressing antiangiogenic proteins.

Regarding 8), Griscelli et al is not used to teach any of the structural limitations of the claimed subject matter. Furthermore, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633